Simulation and Analysis of Noise in Genetic Networks

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Computational models of genetic networks can yield insight into the dynamics of regulation. A fascinating aspect of regulation dynamics is the existence of stochastic fluctuations (i.e., noise) in the intracellular molecular populations and the strategies that cells employ to either minimize or exploit the effect of this noise. Statistically significant noise occurs as a result of the random timing and discrete nature of the transcription, translation, decay, complexation, and binding reactions among a relatively low population of regulatory molecules within the microscopic cell volume. We have developed analysis and simulation tools to understand the relationship between network architecture and the effects of noise.

To demonstrate how a cell can exploit noise, we have simulated the LuxIR quorum sensing (QS) system using Gillespie's exact stochastic simulation algorithm. QS is highly conserved cell-cell communication mechanism that controls population-dependent processes in bacteria such as bioluminescence in *Vibrio fischeri* and virulence factors for cystic fibrosis in *Pseudomonas aeruginosa.* Signaling is achieved by the free diffusion of autoinducer (AI) molecules between cells. AI positively regulates both its own production and that of its receptor protein, so that positive feedback amplifies the QS signal as the cell density increases. Both deterministic and stochastic simulations are shown in Figure 1, utilizing identical model parameters. The deterministic simulation will never become induced since the steady-state AI concentration is below the induction threshold. Induction in the stochastic simulation, signaled by a sharp increase in AI, occurs because noise in the AI population crosses the induction threshold, demonstrating that the noise can be a functional component of the QS system.

In the next example, we use the frequency-domain based analysis tools that we have developed to demonstrate how the noise spectrum is modulated by the simple two-gene network shown in Figure 2. The noise spectrum in the no feed back case is typical for gene circuits where noise is dominated by protein decay. Our analysis shows that negative regulation reduces the low frequency noise at the expense of excess noise higher frequencies. However, this high frequency noise can be filtered out by appropriate downstream circuit elements, resulting in better overall noise performance. We will show that the frequency domain analysis tools provide an intuitive connection between performance and circuit architecture and parameters not possible with simulation.

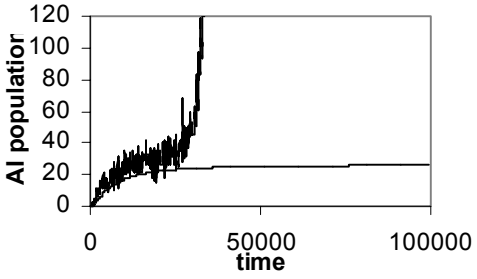
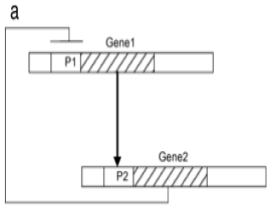


Figure 1. Effect of Noise in QS.



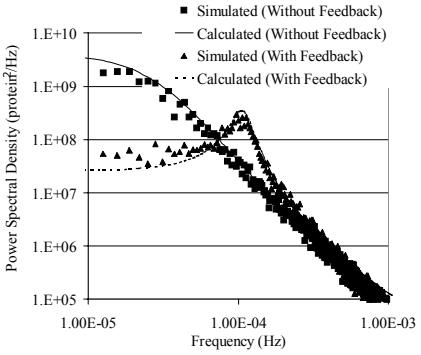


Figure 2. Analysis of Noise Specturm in Two-Gene Circuit

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